CLAIMS

What is claimed is:

1. A method of treating or preventing a myeloproliferative disease, which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of a selective cytokine inhibitory drug, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

2. A method of managing a myeloproliferative disease, which comprises administering to a patient in need of such management a prophylactically effective amount of a selective cytokine inhibitory drug, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

3. A method of treating or preventing a myeloproliferative disease, which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of a selective cytokine inhibitory drug, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, and a therapeutically or prophylactically effective amount of at least one second active agent.

4. A method of managing a myeloproliferative disease, which comprises administering to a patient in need of such management a prophylactically effective amount of a selective cytokine inhibitory drug, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, and a therapeutically or prophylactically effective amount of at least one second active agent.

5. The method of any one of claims 1 to 4, wherein the patient is refractory to a conventional myeloproliferative disease treatment.

6. The method of any one of claims 1 to 4, wherein the patient is refractory to a myeloproliferative disease treatment comprising thalidomide.

7. The method of claims 3 or 4, wherein the second active agent is capable of suppressing the overproduction of hematopoietic stem cells or ameliorating one or more of the symptoms of the myeloproliferative disease.

8. The method of claim 3 or 4, wherein the second active agent is a cytokine, corticosteroid, ribonucleotide reductase inhibitor, platelet inhibitor, anticoagulant, thrombolytic agent, antifibrosis agent, all-trans retinoic acid, kinase inhibitor,

topoisomerase inhibitor, farnesyl transferase inhibitor, antisense oligonucleotide, antibody, agent used to reverse multidrug resistance, vaccine, myelosuppressive agent or anti-cancer agent.

9. The method of claim 8, wherein the second active agent is interferon-α, hydroxyurea, anagrelide, busulfan, arsenic troxide, ST1571, imatinib mesylate, DX-8951f, R115777, vincristine, daunorubicin, prednisone, or a pharmacologically active mutant or derivative thereof, or a combination thereof.

10. The method of any one of claims 1 to 4, wherein the myeloproliferative disease is polycythemia rubra vera, primary thromobocythemia, chronic myelogenous leukemia or agnogenic myeloid metaplasia.

11. The method of any one of claims 1 to 4, wherein the myeloproliferative disease is primary or secondary.

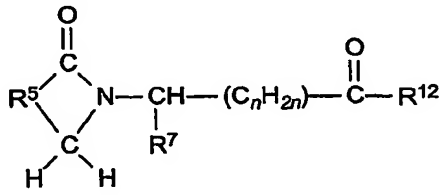
12. The method of any one of claims 1 to 4, wherein the selective cytokine inhibitory drug is 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl) -propionamide.

13. The method of claim 12 wherein the selective cytokine inhibitory drug is enantiomerically pure.

14. The method of any one of claims 1 to 4, wherein the selective cytokine inhibitory drug is cyclopropanecarboxylic acid {2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1 *H*-isoindol-4-yl}-amide.

15. The method of claim 14, wherein the selective cytokine inhibitory drug is enantiomerically pure.

16. The method of any one of claims 1 to 4, wherein the selective cytokine inhibitory drug is of formula (I):



(I)

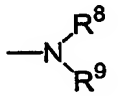
wherein n has a value of 1, 2, or 3;

R^5 is o-phenylene, unsubstituted or substituted with 1 to 4 substituents each selected independently from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy,

carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkylamino, dialkylamino, acylamino, alkyl of 1 to 10 carbon atoms, alkyl of 1 to 10 carbon atoms, and halo;

R^7 is (i) phenyl or phenyl substituted with one or more substituents each selected independently of the other from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, and halo, (ii) benzyl unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of nitro, cyano, trifluoromethyl, carbothoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, and halo, (iii) naphthyl, and (iv) benzyloxy;

R^{12} is -OH, alkoxy of 1 to 12 carbon atoms, or

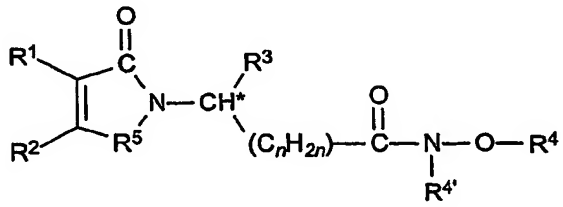


R^8 is hydrogen or alkyl of 1 to 10 carbon atoms; and

R^9 is hydrogen, alkyl of 1 to 10 carbon atoms, $-COR^{10}$, or $-SO_2R^{10}$, wherein R^{10} is hydrogen, alkyl of 1 to 10 carbon atoms, or phenyl.

17. The method of claim 16, wherein the selective cytokine inhibitory drug is enantiomerically pure.

18. The method of any one of claims 1 to 4, wherein the selective cytokine inhibitory drug is of formula (II):



(II)

wherein each of R^1 and R^2, when taken independently of each other, is hydrogen, lower alkyl, or R^1 and R^2, when taken together with the depicted carbon atoms to which each is bound, is *o*-phenylene, *o*-naphthylene, or cyclohexene-1,2-diyl, unsubstituted or substituted with 1 to 4 substituents each selected independently from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl,

carbamoyl, acetoxy, carboxy, hydroxy, amino, alkylamino, dialkylamino, acylamino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, and halo;

R^3 is phenyl substituted with from one to four substituents selected from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, alkylthio of 1 to 10 carbon atoms, benzyloxy, cycloalkoxy of 3 to 6 carbon atoms, C_4-C_6-cycloalkylidenemethyl, C_3-C_{10}-alkylidenemethyl, indanyloxy, and halo;

R^4 is hydrogen, alkyl of 1 to 6 carbon atoms, phenyl, or benzyl;

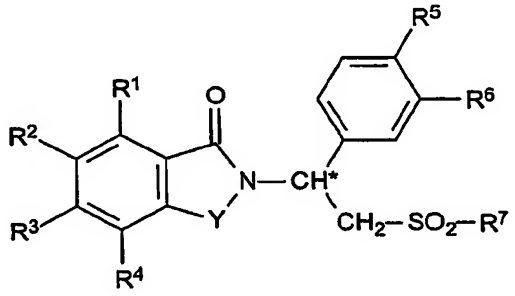
$R^{4'}$ is hydrogen or alkyl of 1 to 6 carbon atoms;

R^5 is $-CH_2-$, $-CH_2-CO-$, $-SO_2-$, $-S-$, or $-NHCO-$; and

n has a value of 0, 1, or 2.

19. The method of claim 18, wherein the selective cytokine inhibitory drug is enantiomerically pure.

20. The method of any one of claims 1 to 4, wherein the selective cytokine inhibitory drug is of formula (III):



(III)

wherein the carbon atom designated * constitutes a center of chirality;

Y is C=O, CH2, SO_2, or $CH_2C=O$;

each of R^1, R^2, R^3, and R^4, independently of the others, is hydrogen, halo, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, nitro, cyano, hydroxy, or $-NR^8R^9$; or any two of R^1, R^2, R^3, and R^4 on adjacent carbon atoms, together with the depicted phenylene ring are naphthylidene;

each of R^5 and R^6, independently of the other, is hydrogen, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, cyano, or cycloalkoxy of up to 18 carbon atoms;

R^7 is hydroxy, alkyl of 1 to 8 carbon atoms, phenyl, benzyl, or $NR^{8'}R^{9'}$;

each of R^8 and R^9 taken independently of the other is hydrogen, alkyl of 1 to 8 carbon atoms, phenyl, or benzyl, or one of R^8 and R^9 is hydrogen and the other is $-COR^{10}$ or $-SO_2R^{10}$, or R^8 and R^9 taken together are tetramethylene, pentamethylene, hexamethylene, or $-CH_2CH_2X^1CH_2CH_2-$ in which X^1 is -O-, -S- or -NH-; and

each of $R^{8'}$ and $R^{9'}$ taken independently of the other is hydrogen, alkyl of 1 to 8 carbon atoms, phenyl, or benzyl, or one of $R^{8'}$ and $R^{9'}$ is hydrogen and the other is $-COR^{10'}$ or $-SO_2R^{10'}$, or $R^{8'}$ and $R^{9'}$ taken together are tetramethylene, pentamethylene, hexamethylene, or $-CH_2CH_2X^2CH_2CH_2-$ in which X^2 is -O-, -S-, or -NH-.

21. The method of claim 20, wherein the selective cytokine inhibitory drug is enantiomerically pure.

22. A method of treating, preventing or managing a myeloproliferative disease, which comprises administering to a patient in need of such treatment, prevention or management a therapeutically or prophylactically effective amount of a selective cytokine inhibitory drug, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, before, during or after transplanting umbilical cord blood, placental blood, peripheral blood stem cell, hematopoietic stem cell preparation or bone marrow in the patient.

23. A method of reducing or avoiding an adverse effect associated with the administration of a second active agent in a patient suffering from a myeloproliferative disease, which comprises administering to a patient in need of such reduction or avoidance a therapeutically or prophylactically effective amount of a selective cytokine inhibitory drug, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

24. The method of claim 23, wherein the second active agent is capable of suppressing overproduction of hematopoietic stem cells or ameliorating one or more of the symptoms of the myeloproliferative disease.

25. The method of claim 23, wherein the second active agent is a cytokine, corticosteroid, ribonucleotide reductase inhibitor, platelet inhibitor, anticoagulant, thrombolytic agent, antifibrosis agent, all-trans retinoic acid, kinase inhibitor, topoisomerase inhibitor, farnesyl transferase inhibitor, antisense oligonucleotide, antibody, agent used to reverse multidrug resistance, vaccine, myelosuppressive agent or anti-cancer agent.

26. The method of claim 25, wherein the second active agent is interferon-α, hydroxyurea, anagrelide, busulfan, arsenic troxide, ST1571, imatinib mesylate, DX-8951f,

R115777, vincristine, daunorubicin, prednisone, or a pharmacologically active mutant or derivative thereof.

27. The method of claim 23, wherein the adverse effect is conversion to acute leukemia; severe myelosuppression; gastrointestinal toxicity; gastrointestinal bleeding; nausea; vomiting; anorexia; leukopenia; anemia; neutropenia; asthenia; abdominal cramping; fever; pain; loss of body weight; dehydration; alopecia; dyspnea; insomnia; dizziness; mucositis; xerostomia; mucocutaneous lesions; or kidney failure.

28. A method of increasing the therapeutic efficacy of a myeloproliferative disease treatment which comprises administering to a patient in need of such increased therapeutic efficacy a therapeutically effective amount of a selective cytokine inhibitory drug, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, and a therapeutically or prophylactically effective amount of a second active agent.

29. The method of claim 28 wherein the therapeutically effective amount of a selective cytokine inhibitory drug, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, is administered prior to administration of the second active agent to a patient.

30. The method of claim 28 wherein the therapeutically effective amount of a selective cytokine inhibitory drug, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, is administered during administration of the second active agent to a patient.

31. The method of claim 28 wherein the therapeutically effective amount of a selective cytokine inhibitory drug, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, is administered after administration of the second active agent to a patient.

32. A pharmaceutical composition comprising a selective cytokine inhibitory drug, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof in an amount effective to treat, prevent or manage a myeloproliferative disease, and a carrier.

33. A pharmaceutical composition comprising a selective cytokine inhibitory drug, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, and a second active agent.

34. The pharmaceutical composition of claim 33, wherein the second active agent is capable of suppressing overproduction of hematopoietic stem cells or ameliorating one or more of the symptoms of a myeloproliferative disease.

35. The pharmaceutical composition of claim 33, wherein the second active agent is a cytokine, corticosteroid, ribonucleotide reductase inhibitor, platelet inhibitor, anticoagulant, thrombolytic agent, antifibrosis agent, all-trans retinoic acid, kinase inhibitor, topoisomerase inhibitor, farnesyl transferase inhibitor, antisense oligonucleotide, antibody, agent used to reverse multidrug resistance, vaccine, myelosuppressive agent or anti-cancer agent.

36. The pharmaceutical composition of claim 35, wherein the second active agent is interferon-α, hydroxyurea, anagrelide, busulfan, arsenic troxide, ST1571, imatinib mesylate, DX-8951f, R115777, vincristine, daunorubicin, prednisone, or a pharmacologically active mutant or derivative thereof, or a combination thereof.

37. A kit comprising:

a pharmaceutical composition comprising a selective cytokine inhibitory drug, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof; and

a pharmaceutical composition comprising a second active agent capable of reversing suppressing overproduction of hematopoietic stem cells.

38. A kit comprising:

a pharmaceutical composition comprising a selective cytokine inhibitory drug, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof; and

umbilical cord blood, placental blood, peripheral blood stem cell, hematopoietic stem cell preparation or bone marrow.

39. A kit comprising:

a pharmaceutical composition comprising a selective cytokine inhibitory drug, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof;

a pharmaceutical composition comprising a second active agent, wherein the second active agent is a cytokine, corticosteroid, ribonucleotide reductase inhibitor, platelet inhibitor, anticoagulant, thrombolytic agent, antifibrosis agent, all-trans retinoic acid, kinase inhibitor, topoisomerase inhibitor, farnesyl transferase inhibitor, antisense oligonucleotide,

antibody, agent used to reverse multidrug resistance, vaccine, myelosuppressive agent or anti-cancer agent; and

umbilical cord blood, placental blood, peripheral blood stem cell, hematopoietic stem cell preparation or bone marrow.

40. The kit of any one of claims 37 to 39 which further comprises a device for the administration of the pharmaceutical composition or the single unit dosage form.